

Long-term efficacy and immunogenicity of the human papillomavirus vaccine

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Introduction

Researchers have performed studies over the past thirty years trying to show the links between human papillomavirus (HPV) infection and cervical cancer (zur Hausen, 2002). Investigations began between the years 1974 and 1976 and during the early 1980's the first HPV types, HPV 16 and HPV 18, were found to be present in cervical cancer biopsy samples (zur Hausen, 1977). The laboratory of Meisels and Fortin (1976) subsequently published two articles highlighting the existence of koilocytes in cervical cancer samples that designated the presence of HPV infection. Koilocytes are altered cervical cells generated by an infection with HPV. These cells acquire an "owl-eye" shape caused by shrinking of the nucleus and a "translucent halo" that encircles the nucleus. These changes in cellular morphology were the beginning of dysplasia that caused cervical malignancies (Meisels & Fortin, 1976).

There have also been advances since the 1980's in the methodology researchers have used to prove the causal relationship between HPV infection and cervical cancer. Epidemiological studies are imperative to form a relationship between the risk factors for development of cervical pathology and cervical cancer. Originally comparisons were made between patients with cervical cancer and control groups based on questionnaires (Bosch, Lorincz, Munoz, Meijer & Shah, 2002). Now with the availability of HPV DNA detection technology, it is possible to establish scientifically sound comparisons between high-risk patients and control groups. With this advancement, HPV DNA has been detected in 90-100% of cervical cancer cases compared with only 5-20% of cervical samples taken from women in control studies (Bosch, Lorincz, Munoz, Meijer & Shah, 2002). By being able to prove the involvement of HPV in the development of cervical cancer, this cancer has become one of the

only human cancers with a direct causal relationship to a particular infection (Bosch, Lorincz, Munoz, Meijer & Shah, 2002).

HPV infection and its possible sequelae have been an area of great interest in the medical community due to the unique nature of the relationship of the virus and the pathologies it causes. Cancers of the anogenital region and genital warts have been proven to have a very strong causal relationship with infection by various types of HPV (Harper, Franco, Wheeler, Moscicki, Romonowski, & Roteli-Martins et al., 2006). As a result, prevention and screening have been in the forefront of management for HPV-related illnesses. By establishing this link between HPV infection and cervical cancer, there has been motivation to create a prophylactic vaccine against the most common forms of the virus associated with the development of cervical cancer; HPV 16 and HPV 18 (Harper et al., 2006). Vaccinations against HPV infection have been developed and on the market since 2006 (J. Dillner, Arbyn & L. Dillner, 2007).

Problem statement

Infection with HPV has been proven to have a causal relationship with cervical cancer and other anogenital pathologies. A quadrivalent vaccine has been developed in recent years with aims to prevent infection and disease caused by four common HPV types. Even though efficacy and immune memory has been shown through five years of vaccine implementation, additional studies are needed to explore long-term effects of the vaccine.

Purpose

The purpose of this study is to evaluate the current studies of efficacy and immunogenicity of the quadrivalent HPV vaccine. In addition, it is also imperative to focus on the long-term effectiveness of the vaccine in order to determine antibody immune response and the possible need for booster vaccinations.

Scope

Articles from peer-reviewed journals will be used to discuss the topic of HPV infection, cervical cancer, and the quadrivalent HPV vaccine. Articles were chosen that have been written since the year 1975 to the present. The scope of research consisted of the pathology of HPV infection and corresponding sequelae, physiology of the HPV vaccination, current recommendations for the administration of the HPV vaccine.

Design

The design of this study is a comprehensive literature review. It incorporates studies and research performed regarding HPV infection, cervical cancer, and the quadrivalent HPV vaccine.

Literature review

It has been shown that 30-50% of the population of the United States has tested positive for HPV in the anogenital area (Brinkman, Hughes, Stone, Caffrey, Muderspach, & Roman et al., 2007). This ranks HPV near the top for the most common sexually transmitted infections (Brinkman et al., 2007). In a study by Walboomers, Jacobs, Manos, Bosch, Kummer, & Shah et al. (1999), it was shown that 99.7% of all cervical carcinomas were found to be linked to HPV. This proved that cervical cancer, which is the cancer ranked second worldwide for causing the highest mortality in women, is vastly associated with infection by HPV (Brinkman et al., 2007). On a global scale, about 510,000 incident cases and 288,000 deaths from cervical cancer are reported every year (World Health Organization, 2004). In the United States cervical cancer is the tenth most common cancer-related cause of death in women with approximately 13,000 new cases and 4,500 deaths annually (Saslow, Runowicz, Solomon, Moscicki, Smith, & Eyre, 2004). Along with cervical cancer, human papillomaviruses are also known to cause associated pre-cancerous lesions and genital warts (Francheschi, 2005).

Multiple risk factors have been identified in regards to HPV infection and cervical cancer. Younger age of first sexual intercourse and increased number of sexual partners are two risk factors reported in numerous studies (Basemen & Koutsky, 2005). There also exists considerable socioeconomic, racial, and ethnic disparities associated with incidence, mortality, and survival connected with cervical cancer in the United States (Singh, Miller, Hankey & Edwards, 2004).

By establishing the relationship between HPV and cervical cancer, a vaccination has been developed as prophylaxis and protection against the most common types of the HPV. The company Merck Sharp and Dohme developed a quadrivalent vaccine containing HPV types 6, 11, 16, and 18. It was approved by the United States Food and Drug Administration on June 8, 2006 for use in females between the ages of nine and twenty-six years of age (J. Dillner, Arbyn & L. Dillner, 2007). The accepted indications of the vaccine include protection against genital warts, cervical cancer, cervical adenocarcinoma in situ, cervical intraepithelial neoplasia grades I, II, and III, vulvar intraepithelial neoplasia grades II and III, and vaginal intraepithelial neoplasia grades II and III caused by the four types of HPV in the vaccine (J. Dillner, Arbyn & L. Dillner, 2007).

In addition to the prophylactic vaccination, screening for precancerous lesions has been shown to decrease the burden of cervical cancer in the United States (Basemen & Koutsky, 2005). The HPV vaccine is aimed at protection for individuals who have not been exposed to the virus and only protects against four specific types. For this reason, routine screening by the cytologic Papanicolaou smear is still a necessary medical intervention (J. Dillner, Arbyn & L. Dillner, 2007).

Research question/hypothesis

Are the current interventions and prevention strategies aimed at lowering the incidence and prevalence of HPV infection and cervical cancer effectively decreasing the number of women in the United States contracting these diseases? Is it necessary to further develop a public health initiative and education program designed to decrease the burden of HPV infection and cervical cancer in women throughout the United States?

Definitions

Human papillomavirus (HPV): A DNA virus that is transmitted by skin-to-skin contact. Some

HPV types cause warts, while others may cause cancerous and precancerous lesions.

Over 40 types of HPV have been identified (Bosch, Lorincz, Munoz, Meijer, & Shah, 2002).

Vaccination: The administration of antigenic material to produce immunity to a disease (J.

Dillner, Arbyn, & L. Dillner, 2007).

Cervix: The lower, narrow portion of the uterus where it joins with the top end of the vagina

(Ho, Bierman, Beardsley, Chang, & Burk, 1998).

Methodology

Articles were found through the use of PubMed and Medline databases. Search terms included human papillomavirus/HPV, HPV vaccine, and cervical cancer.

Literature Review

Human papillomavirus and sequelae

Pathogenesis of HPV infection

It has been shown that an individual's immune system plays an important role in controlling HPV infections (zur Hausen, 2002). This conclusion has been inferred indirectly from showing that there is extended persistence and increased incidence of squamous intraepithelial lesions in women who are immunosuppressed (Petry, Scheffel, Bode, Gabrysiak, Kochel, & Kupsch et al., 1994). Studies have also shown that there is the presence of helper T cells in cervical lesions that are regressing and involvement of a humoral immune reaction against HPV antigens (Jenson, Kurman & Lancaster, 2000). Chardonnet, Viac, Staquet, and Thivolet (1985) were able to demonstrate the presence of helper T cells by investigating the cellular immune response in cervical lesions and anogenital warts. They used monoclonal antibodies for helper T cells, circulating T cells, and cytotoxic T cells on 60 samples of HPV-infected tissue and found T cells to be present in all specimens (Chardonnet, Viac, Staquet & Thivolet, 1985). Furthermore, they also showed the incidence of lesions caused by HPV increased in patients who were currently on immunosuppressive therapy or had malignant immunological diseases, such as chronic lymphatic leukemia (Chardonnet, Viac, Staquet & Thivolet, 1985). The ability of the HPV infection to progress to dysplasia has been closely linked to the capability of the virus to escape from normal physiological immune system regulation (zur Hausen, 2002).

The acknowledged pathway in cervical carcinogenesis begins with infection by an oncogenic type of HPV, progression to a high-grade squamous intraepithelial lesion, advancement to carcinoma in situ, and finally a fully invasive form of cervical cancer (Basemen

& Koutsky, 2004). Low-grade squamous intraepithelial lesions are a temporary viral infection and occur when the epithelial cells infected with HPV differentiate and mature but only exhibit slight cellular irregularities (Basemen & Koutsky, 2004). High-grade squamous intraepithelial lesions, which are the precursors to cervical cancer, occur through infection of immature basal epithelial cells; therefore causing the cells to replicate while not fully developed and genetic abnormalities accumulate, ultimately leading to the cloning of cancerous cells (Basemen & Koutsky, 2004). Low-grade squamous intraepithelial lesions are most often found in locations more distal from the cervical os, whereas high-grade squamous intraepithelial lesions are frequently located more proximally (Basemen & Koutsky, 2004).

Human papillomaviruses are nonenveloped icosahedral-shaped capsids with a 55 millimeter diameter that surround a double-stranded genome of DNA that is around eight thousand base pairs long (Munger, Baldwin, Edwards, Hayakawa, Nguyen, & Owens et al., 2004). Human papillomaviruses are unable to encode for proteins to make their own enzymes and are critically dependent on using the host cell's cellular machinery for proliferation (Munger et al., 2004). An important step in the life cycle of the human papillomavirus is the necessity for the virus to use basal mucosal or epidermal epithelial cells in order to replicate (zur Hausen, 2002). Once initial viral infection occurs, three specific oncogenes are produced and cause much of the dysplastic cellular growth: oncogenes E5, E6, and E7 (zur Hausen, 2002). Oncogene E5 is responsible for inciting increased cellular growth by forming complexes with three specific receptors: colony stimulating factor receptor, platelet derived growth factor β receptor, and the epidermal growth factor receptor (zur Hausen, 2002). Oncogene E5 also plays a role in hindrance of cellular apoptosis that should naturally occur once any host cellular DNA damage has occurred (zur Hausen, 2002). Oncogenes E6 and E7 are more closely related to the

malignant processes that HPV infection can cause because they actively obstruct cell cycle control mechanisms (Brinkman et al., 2007). Protein p53 is necessary for repairing any damage to DNA and is a mediator in the G1 cell cycle step of suspending cellular growth or apoptosis when the cell has incurred considerable DNA damage; the ultimate result is accumulation of genetic mutations and cellular instability (Favre, Ramoz & Orth, 1997). Oncogene E6 has been shown to interfere with the normal function of p53 (Werness, Levine & Howley, 1990). The E7 oncoprotein interacts with the retinoblastoma tumor suppressor protein; the effect is poor regulation of the cell cycle and inability to properly direct basal epithelial cell proliferation (Brinkman et al., 2007). The three oncogenic proteins E5, E6, and E7 have been steadily found in malignant tissue biopsy samples of cervical cancer (zur Hausen, 2002). Malignant phenotype of cervical cancer cells has been successfully inhibited if the expression of the three genes has been blocked (zur Hausen, 2002).

Background of HPV and cervical cancer

HPV infection is a very common infection. Even with this reality, a large percentage of infected people clear the virus before it causes clinically significant pathologies (Basemen & Koutsky, 2005). For those women who cannot clear the viral infection simply through their immune processes, multiple possible medical sequelae can result. More than forty types of HPV have been detected and are known to infect the human anogenital region (zur Hausen, 1996). The various HPV types have been classified according to their severity of risk associated with advancement to cervical cancer: fifteen are categorized as high-risk for development of cervical cancer, three are probable high-risk, twelve are considered low risk, and three are classified as undetermined risk (Munoz, Bosch, de Sanjose, Herrero, Castellsague, & Shah et al., 2003). Those included in the high risk human papillomavirus category include HPV 16, 18, 31, 33, 35,

39,45, 51, 52, 56, 58, 59, 68, 73, and 82; probable high-risk types include HPV 26, 53, and 66; low risk HPV types are 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108; and the HPV types considered undetermined risk are 34, 57, and 83 (Munoz et al., 2003).

Globally, the second most common cancer in women is cervical cancer (Ries, Eisner, Kosary, Hankey, Miller, & Clegg et al., 2004) and mortality from cervical cancer ranks third worldwide (Pecorelli, Favalli, Zigliani, & Odicino, 2003). Since 2000, there has been an average of 470,000 incident cases of cervical cancer across the world every year (Baseman & Koutsky, 2005). The average age for diagnosis of cervical cancer is forty-seven years old, which is typically ten to twenty years after the HPV infection occurs (Markowitz, Dunne, Saraiya, Lawson, Chesson, & Unger et al., 2007). In addition, 3.5 to 5 million women each year have abnormal Papanicolaou smears and necessitate procedures for prevention of progression to cervical cancer (Ohri, 2007).

Annually in the United States there are approximately 6 million new cases of active genital HPV infections (Weinstock, Berman & Cates, 2004). It is estimated that 20 million residents of the United States have existing HPV infections; this is approximately 15% of the country's population and just under half of these infections occur in people between the ages of fifteen and twenty-five years of age (Koutsky, 1997). According to Myers, McCrory, Nanda, Bastian, and Matchar (2000), over half of sexually active people will become infected with HPV throughout their lifetime and 80% of sexually active women are infected by age fifty.

In a study conducted with patients from Planned Parenthood, it was shown that prevalence of infection with high-risk HPV was 27.4% in women with a median age of twenty-five years of age (Kulasingam, Hughes, Kiviat, Mao, Weiss, & Kuypers et al., 2002). The study was performed between December 1997 and October 2000 in the state of Washington and 4075

Planned Parenthood patients who presented for their annual examination were screened through the use of Papanicolaou smears and detection of high-risk HPV DNA through polymerase chain reaction (Kulasingam et al., 2002). The requirements for participation included being between 18 and 50 years of age, no previous treatment for cervical dysplasia or malignancy, no history of hysterectomy, and no history of a chronic immunosuppressive disease (Kulasingam et al., 2002). Abnormal Papanicolaou tests were found in 678 of the 4075, or 16.6% of the participants, and the polymerase chain reaction detected high-risk HPV DNA in 747 of the 4075 women, which is 18.3% of participants (Kulasingam et al., 2002). The most common type of HPV detected by polymerase chain reaction was type 16; it was detected in 214 of the 747 women positive for HPV DNA, which is 28.7% of this group (Kulasingam et al., 2002). Two prevalence estimates were made, one before 2000 and one after the year 2000, and the weighted estimate of these two together was 27.4% (Kulasingam et al., 2002). Also, prevalence was found to be similar amongst female college students (Richardson et al., 2003). Richardson, Kelsall, Tellier, Voyer, Abrahamowicz, and Ferenczy et al. (2003) had 635 women in their study that was performed between 1996 and 1999 at McGill University in Montreal. These women had an average age of 23 years old and 45% of them reported they have had five or more sexual partners in their lifetime (Richardson et al., 2003). The women were given an initial screening for HPV infection through DNA polymerase chain reaction of cervical cell samples and had serial screening every six months for two years. At the conclusion of the study, the prevalence of HPV infection was 29.0% for all the participants (Richardson et al., 2003).

Woodman, Collins, Winter, Bailey, Ellis and Prior et al. (2001) conducted a study that showed that over a three-year period the incidence of infection with HPV in women was 44%. The study by Woodman et al. (2001) was done between the years of 1988 and 1992 and enrolled

2011 sexually active young women between the ages of 15 and 19 years old. Of this group, 1075 were found to be negative for HPV infection and have no cervical cytological abnormalities at enrollment in the study (Woodman et al., 2001). Cervical Papanicolaou smears were given to each participant at six-month intervals for continued surveillance (Woodman et al., 2001). After three years 44% (95% CI 40-48) were infected with a type of HPV that was not detected at the initiation of the study (Woodman et al., 2001). A comparable outcome was found in another study by Ho, Bierman, Beardsley, Chang and Burk (1998) with 608 female college students in New Jersey. These women were followed at six-month intervals for three years. At each visit cervical cytological samples were obtained for DNA polymerase chain reaction studies and hybridization with Southern blot technique. Papanicolaou smears were also performed annually. At the conclusion of 36 months of surveillance, the incidence rate of HPV infection was 43% (95% CI 36-49) (Ho, Bierman, Beardsley, Chang & Burk, 1998).

Diseases caused by HPV

HPV types 16, 18, 31, 33, and 45 have a causal relationship with malignancies of the anogenital region, which includes cervical, vaginal, vulvar, anal, and penile cancers (Koutsky, Galloway & Holmes, 1988). HPV types 16 and 18 are accountable for approximately 70% of invasive cervical malignancies (Munoz et al., 2003). Globally, HPV type 18 is responsible for 17% of cervical cancer and HPV type 16 causes 54% of cervical malignancies (Munoz et al., 2003). Four thousand Americans are diagnosed annually with anal cancer and between fifty and sixty percent of these cases are associated with HPV types 16 and 18 (Moscicki, Shiboski, Broering, Powell, Clayton, & Jay et al., 2006). Of these cases of anal cancer, there are a resulting 620 deaths each year (Kyrgiou, Tsoumpou, Vrekoussis, Martin-Hirsch, Arbyn, & Prendiville et al., 2006). Cases of vulvar cancer annually total 3,870 with 870 deaths and 40% of

these are related to HPV infection (Wideroff, Schiffman, Haderer, Armstrong, Greer, & Manos et al., 1999).

Human papillomaviruses are the cause of squamous cell cervical cancer and cervical adenocarcinoma; the viruses are also the causes of cervical cancer precursor lesions. The precursor lesions include cervical intraepithelial neoplasia grade one or low-grade dysplasia, cervical intraepithelial neoplasia grades two and three or moderate to high-grade dysplasia, and adenocarcinoma in situ (Miller, Raychaudhuri, & Toerner, 2007). Human papillomaviruses cause 35-50% of vaginal and vulvar cancers. The papillomaviruses are also responsible for vaginal intraepithelial neoplasia grades two and three and vulvar intraepithelial neoplasia grades two and three; these kinds of neoplasia are precursor cells to the corresponding cancers (Merck, 2006). Saslow, Castle, Cox, Davey, Einstein, and Ferris et al. (2007), along with help from the American Cancer Society, reported that 70% of cervical cancers are caused by HPV types 16 and 18.

The incidence of high-grade squamous intraepithelial lesions have been shown to be associated with oncogenic forms of HPV (Baseman & Koutsky, 2005). A study by Koutsky, Holmes, Critchlow, Stevens, Paavonen, and Beckmann et al. (1992) demonstrates the point that high-grade cervical intraepithelial neoplasia is tightly linked to the presence of HPV infection. A longitudinal study performed at a clinic in Seattle, Washington randomly enrolled 779 women between the ages of 16 and 50 years old that presented with a chief complaint of possible sexually transmitted disease (Koutsky et al., 1992). These women were examined every four months by cytological and colposcopic methods and given tests for detection for HPV DNA. It was shown that a group of women who had no previous history of squamous intraepithelial lesions also showed a two-year incidence of high-grade cervical intraepithelial neoplasia grade II

or III confirmed by biopsy to be 28% in women who were positive for HPV and 3% in women with no detectable HPV infection (Koutsky et al., 1992). HPV types 16 and 18 were found to be present in 18% of the women who developed the high-grade cervical intraepithelial neoplasia grade II and III and were the types responsible for the largest proportion of the disease. (Koutsky et al., 1992). Similar results were found in another study performed by Woodman, Collins, Winter, Bailey, Ellis, and Prior et al. (2001). The conclusion of Woodman and his colleagues showed that women who were negative for both squamous intraepithelial lesions and HPV infection at initial enrollment in the experiment and then become infected with HPV were 13 times more likely to be diagnosed with high-grade squamous intraepithelial lesions than women who remained HPV-negative (Woodman et al., 2001)

More than half a million incident cases of anogenital warts are diagnosed every year in the United States and approximately 90% of genital warts are caused by HPV types 6 and 11 (J. Dillner, Arbyn & L. Dillner, 2007). Greer, Wheeler, Ladner, Beutner, Coyne, and Liang et al. (1995) studied a group of 39 patients with genital warts. They found that 94% were positive for HPV type 6 (95% CI 82-99) and 8% had lesions positive for HPV type 11 (95% CI 2-22). Giant condylomas are associated with infection by HPV types 6 and 11 and can possibly, although uncommon, progress to form malignancies known as Buschke-Lowenstein tumors of the penis, vulva, and anus (Cogliano, Baan, Straif, Grosse, Secretan & El Ghissassi, 2005).

Vaccination against human papillomavirus infection

Formulation of the vaccination

Now that there has been a proven link between infection with HPV and cervical cancer and other genital diseases there is also the potential to prevent these illnesses through vaccination. Research has been conducted recently to formulate an appropriate vaccine for this

purpose. The vaccine includes the most common HPV types associated with genital diseases, HPV types 6, 11, 16, and 18 (J. Dillner, Arbyn, & L. Dillner, 2007). The discovery of the viral etiology of cervical pathology and development of a prophylactic vaccination presents the opportunity for universal cervical cancer prevention.

The prophylactic vaccination contains virus-like particles (VLPs) and the L1 gene capsid protein of the four included types of HPV (Brinkman, Hughes, Stone, Caffrey, Mudersach, & Roman et al., 2007). The HPV L1 VLPs are antigens that resemble the viral capsid and are arranged in a specific conformational manner (Brinkman et al.). The HPV L1 VLPs are devoid of the viral DNA and therefore the vaccine does not contain live attenuated viruses (Pinto, Edwards, Castle, Harro, Lowy, & Schiller, 2003). Exposing the body's natural immune response to these L1 VLPs causes the production of type-specific antibodies that have the potential to combat future infection with the four included types of HPV (Zhou, Sun, Stenzel, & Frazer, 1991).

The quadrivalent HPV vaccine is composed of L1 VLPs of types 6, 11, 16, and 18 (Ault, Giuliano, Edwards, Tamms, Kim, Smith, et al., 2004). The current approved and marketed dose contains 20 micrograms of HPV type 6 L1 VLP, 40 micrograms of HPV type 11 L1 VLP, 40 micrograms of HPV type 16 L1 VLP, and 20 micrograms of HPV type 18 L1 VLP (Olsson, Villa, Costa, Petta, Andrade, Malm, et al., 2007). The multiple HPV types are combined with 225 micrograms of amorphous aluminum hydroxyphosphate sulfate and make a total injection volume dosage of 0.5 milliliters (Olsson et al.).

Initial vaccine studies

Beginning in 2002 a three-phase trial was performed to assess the efficacy of a quadrivalent vaccine aimed at preventing HPV types 6, 11, 16, and 18 (Garland, Hernandez-

Avila, Wheeler, Perez, Harper, Leodolter, et al., 2007). The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE I) study was sponsored by the pharmaceutical company Merck Sharpe and Dohme to evaluate the vaccine (Garland et al., 2007). There were 6463 women between the ages of 16 and 24 screened for eligibility within the first year of the study (Garland et al). Inclusion criteria included women who were not pregnant, had no history of genital warts or abnormal Pap smears, and had four or less lifetime sexual partners. All participants were required to use effective contraception during the vaccination period. A total of 5455 women were accepted into the study (84%) and were selected from 62 clinical sites in 16 different countries. Through a randomization process 2723 women were included in the group to receive the quadrivalent vaccine and 2732 women were assigned to the placebo group. At the onset of the study only 8 women (0.15%) were serologically positive for HPV DNA with all four types of HPV covered by the vaccine. Injections were given at day one, at month two and at month six and follow up was continued for three years. Gynecologic examinations were performed at day one and months seven, 12, 24, and 36. HPV DNA testing and HPV antibody testing was performed on cervical, labial, perineal, and perianal swab specimens at day one and months three, seven, 12, 18, 24, 30 and 36. Women were observed for 30 minutes following the administration of the vaccine for side effects. The participants recorded oral temperatures four hours after the vaccination and daily for the subsequent four days. The participating women recorded any adverse events for 15 days following vaccination.

By the end of the three-year trial just over 83% of the participants were still enrolled in the study (Garland, Hernandez-Avila, Wheeler, Perez, Harper, & Leodolter, 2007). The vaccine group contained 2261 subjects and reported zero cases of anogenital pathology. The placebo group had 2279 subjects and reported 60 cases of anogenital pathology. The quadrivalent HPV

vaccine was shown to be 100% effective (95% CI 94-100) in the prevention of vaginal, vulvar, perineal, and perianal intraepithelial lesions and warts associated with HPV types 6, 11, 16 and 18. Also 99.5% of subjects in the vaccine group exhibited seroconversion of anti-HPV antibodies at month seven, which was one month following the third dose of the vaccine. The overall results of this study showed that anogenital diseases caused by HPV types 6, 11, 16, and 18, including genital warts and intraepithelial neoplasia of the vulva, vagina, and cervix, are preventable through use of a prophylactic quadrivalent HPV vaccination.

The safety of the HPV vaccination was also investigated during the preliminary studies. There were minor adverse events associated with the administration of the vaccine. Side effects at the site of injection were reported in 83% of the group receiving the vaccine and in 73.4% of the placebo group (Villa, Costa, Petta, Andrade, Paavonen, Iversen et al., 2006). Adverse events at the injection site included swelling, erythema, and pain, which all were reported to have increased severity in the participants receiving the vaccine (Villa et al). Systemic complaints such as fever, headache, and nausea were reported by 69% of vaccine recipients. There were no deaths during the study period that were a consequence of the vaccination or the procedures performed. Serious adverse events in the vaccine group that occurred during the trials included one case of bronchospasm, one case of gastroenteritis, one case of headache accompanied by hypertension, one case of joint movement impairment near the injection site, and one case of vaginal hemorrhage. Within the placebo group the serious adverse events reported included one case of severe hypersensitivity and one case of fever, chills, and headache. Adverse events caused only 0.2% of participants in both the vaccine and placebo groups combined to discontinue the study (Villa et al).

Prior to application for approval by the Food and Drug Administration, three additional randomized double-blind studies were also performed regarding the HPV vaccination (Villa, Costa, Petta, Andrade, Paavonen, Iversen et al., 2006). A Phase II study, known as Protocol 005, assessed only the HPV type 16 component of the vaccine. Another Phase II study, termed Protocol 007, evaluated all four types of HPV included in the vaccine. Finally, another Phase III trial in addition to the FUTURE I trial was performed and known as the FUTURE II study. Both of the FUTURE trials tested the form of the quadrivalent vaccine that would eventually be approved and marketed under the name Gardasil. With all four studies combined, 20,541 women between the ages of 16 and 26 took part in these trials. In all of the studies, the participants were randomly assigned to receive injections of the vaccine or placebo at zero, two and six months. Analysis of efficacy was done individually for each study and for all studies combined. Results of each study and the analysis of efficacy of the quadrivalent HPV vaccine are displayed in Table 1 (Villa et al).

Following the approval and licensing of the quadrivalent HPV vaccine Gardasil, the American Cancer Society established a set of recommendations for the use of the vaccine to prevent cervical cancer and its precursors (Saslow, Castle, Cox, Davey, Einstein, & Ferris et al., 2007). These guidelines state that the routine use of the HPV vaccine is recommended for females between the ages of 11 to 12 years old and can be given to females as young as 9 years of age. The HPV vaccine is also suggested to women between the ages of 13 and 18 years old if needed to catch up on the vaccine regimen. The American Cancer Society states that the decision to vaccinate women between the ages of 19 and 26 years old should be based on clinical discretion regarding the female's risk of preceding HPV contact and what level of potential

benefit it may afford. Currently the HPV vaccination is not advised or approved for females over 26 years of age or for males.

Immune memory and prolonged efficacy of the HPV vaccine

The basis of using vaccines to prevent the development of particular diseases lies in the concept of inducing the body's own immune system to create an immune memory against an offending antigen. For a vaccine to be effective in providing long-term protection and disease prevention it must stimulate the production of memory immune cells that will create a potent immune response if there is exposure to antigenic material (Villa, Ault, Giuliano, Costa, Petta, & Andrade et al., 2006).

A five-year follow-up study was performed and aimed at investigating the prolonged efficacy following the administration of the quadrivalent HPV vaccine (Villa, Costa, Petta, Andrade, Paavonen & Iversen, 2006). To date this is the longest study done on the HPV vaccination. This study was arranged in the same way as the Phase II Protocol 007 initial study performed. The focus of the study looked at disease end points in vaccine-receiving groups and placebo-receiving groups after five years. The study included 552 women between the ages of 16 and 23 years of age to take part in the initial three years of the study. The HPV vaccine was given to 276 participants and the placebo was given to 275 of the women at day zero, month two, and month six. Follow-up was conducted from month seven to month 36 for this cohort of women. Follow-up included Pap testing, anogenital swabbing and analysis, and serum collection and analysis. At the conclusion of the three-year follow-up, 241 women were enrolled in a two-year extension follow-up study to further investigate prolonged efficacy and immunogenicity. Five years after the beginning of the study, the incidence of infection or disease caused by HPV types 6, 11, 16, and 18 declined by 96% in the population of women who received the HPV

vaccine as compared to the placebo group. There were two reported cases of HPV-related disease in the vaccine group and 46 cases in the placebo group. There was also an analysis of disease end points base on the specific type of HPV that caused the disease. For the two cases that involved the vaccine group, there was one reported case of infection with HPV 16 and one case of infection with HPV 18. Neither infection proceeded to cause cervical dysplasia. In the placebo group there were 45 women with infection, three that had developed CIN I-III, and three with condyloma. Of these cases, 17 were related to infection with HPV 6, three related to HPV 11, 28 related to HPV 16, and 11 related to infection with HPV 18. A complete list presenting the results of this study is shown in Table 2. This study supports the idea that the quadrivalent HPV vaccine will sustain long-term efficacy and prevention of anogenital diseases caused by the four types of HPV included in the vaccine.

Another study that was recently performed focused on the strength of the immune memory response upon exposure to the HPV antigens (Olsson, Villa, Costa, Petta, Andrade, & Malm et al., 2007). The study investigated how well the vaccine could produce immune memory that was HPV type-specific. This study began with the same participants that were involved in the Protocol 007 study. After the initial rounds of administration of vaccine or placebo at day zero, month two, and month six, 241 women were selected to participate in this specific five-year follow up study. This group of women involved in the extension study received the three primary injections of the HPV vaccine, were seronegative for HPV antibodies and PCR-negative for HPV DNA at enrollment in the study, and continued to be HPV DNA PCR-negative through month 60 of the study. Levels of type-specific HPV antibodies were recorded at month seven, one month following the administration of dose three of the vaccine. Measurements were recorded in geometric mean titers (GMT). Type-specific antibodies were then also measured at

month 60. Following the month 60 measurement the subject was re-challenged by the HPV antigen by being given another dose of the vaccine. HPV type-specific antibodies were then again measured one week following this administration and at month 61. This re-challenge with HPV antigen produced a considerable immune response as shown by a large increase in the GMTs of all four HPV antibody types. HPV antibody GMTs were highest at month seven following the final dose of the vaccine regimen. Anti-HPV GMTs fell after month seven but then reached a stable state by month 24 and stayed at this plateau through the five years of the extension study. Results of GMT studies for each HPV type are shown in Table 3. This study shows that the quadrivalent HPV vaccine has the ability to induce a powerful immune response through at least five years following administration. Even though there is no definition of the minimum level of HPV antibodies needed to cause protective efficacy of the vaccine, this study gives some evidence that the vaccine will be able to provide long-term protection against HPV-related diseases.

Conclusion

Current studies have shown promise for the possibility of eradication and decline in the cervical malignancies and other HPV-related pathologies. It has been estimated that if women were given the quadrivalent HPV vaccine before their sexual debut there could be a decrease in the risk of anogenital and cervical cancer by at least 85% and a 44-70% decrease in the amount of abnormal Pap smears caused by HPV (Walboomers, Jacobs, Manos, Bosch, Kummer, & Shah, 1999). It has also been thought that if the HPV vaccine were available globally it has the potential to prevent over 300,000 incident cases annually (zur Hausen, 2002). Overall, morbidity and mortality associated with HPV-related diseases could be dramatically decreased through the use of the prophylactic HPV vaccine.

Although the current studies through five-year follow-up show great promise for the efficacy and immunogenicity of the HPV vaccine, there still remain many questions unanswered. Due to the fact that it takes an extended period of time for progression of HPV infection and cervical cancer, it will take a considerable amount of time before the actual effects on morbidity and mortality will be realized. It has been suggested that even after vaccination programs are effectively executed, it will be at least a decade before a reduction in the incidence of cervical cancer will be apparent (Crum, 2002).

In the meantime it is important for physician assistants to play an appropriate role in helping to implement the HPV vaccine and reduce the incidence of all HPV-related pathologies. One of the most important concepts at this time is the continuance of cervical screening recommendations. Even with the promise shown by the HPV vaccine, any hasty reduction of routine gynecological examinations and Pap smears could have the potential to cause cervical cancer rates to rise. It is also imperative to educate patients that the HPV vaccine does not

provide protection against all strains of carcinogenic HPV so it is necessary to perform the recommended screenings.

Overall, the rates of cervical cancer and HPV-related diseases depend on multiple factors related to the HPV vaccine. It will be necessary to continue studies on the long-term efficacy and immunogenicity of the HPV vaccine and also determine if there will be a need for booster vaccines. Reduction in HPV-related anogenital pathology also depends on the widespread availability of the vaccine to at-risk populations.

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Table 1
Efficacy Analysis of Quadrivalent HPV Vaccine

	Quadrivalent HPV vaccine		Placebo		% Efficacy (95% CI)
	n	# of cases	n	# of cases	
HPV 16- or 18-related CIN II/III or AIS					
Protocol 005	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (-3734.9, 100.0)
FUTURE I	2200	0	2222	19	100.0 (78.5, 100.0)
FUTURE II	5301	0	5258	21	100.0 (80.9, 100.0)
HPV 6-, 11-, 16-, 18-related CIN (CIN I, CIN II/III) or AIS					
Protocol 007	235	0	233	3	100.0 (-137.8, 100.0)
FUTURE I	2240	0	2258	37	100.0 (89.5, 100.0)
FUTURE II	5383	4	5370	43	90.7 (74.4, 97.6)
HPV 6-, 11-, 16-, 18-related genital warts					
Protocol 007	235	0	233	3	100.0 (-139.5, 100.0)
FUTURE I	2261	0	2279	29	100.0 (86.4, 100.0)
FUTURE II	5401	1	5387	59	98.3 (90.2, 100.0)

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Table 2
Efficacy of Quadrivalent HPV Vaccine at Five-Year Follow-Up

	Vaccine		Placebo			
End point	n	Cases	n	Cases	Efficacy (%)	95% CI (%)
<i>Infection or disease</i>	235	2	233	46	95.8	(83.8, 99.5)
Infection	235	2	233	45	95.6	(83.3, 99.5)
Disease	235	0	233	6	100.0	(12.4, 100.0)
CIN I-III	235	0	233	3	100.0	(<0.0, 100.0)
Condyloma	235	0	233	3	100.0	(<0.0, 100.0)
<i>End points by HPV type</i>						
HPV 6	214	0	209	17	100.0	(75.7, 100.0)
HPV 11	214	0	209	3	100.0	(<0.0, 100.0)
HPV 16	199	1	198	28	96.6	(79.2, 99.9)
HPV 18	224	1	224	11	90.6	(35.6, 99.8)

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Table 3

Average Geometric Mean Titers Comparing Type-Specific HPV Antibodies From Month Seven to Re-challenge at Month 60

	GMT (mMu/mL)	95% CI
HPV 6		
Month 7	549.2	(460.6, 654.7)
Month 60 (pre-challenge)	67.7	(53.5, 85.7)
Month 60 + 1 week	503.3	(344.2, 736.1)
Month 61	693.2	(451.9, 1063.3)
HPV 11		
Month 7	635.5	(521.3, 774.9)
Month 60 (pre-challenge)	70.1	(52.5, 93.7)
Month 60 +1 week	1417.5	(1009.0, 1991.4)
Month 61	2652.4	(1956.7, 3593.3)
HPV 16		
Month 7	3870.0	(3157.0, 4744.0)
Month 60 (pre-challenge)	404.2	(312.9, 522.1)
Month 60 + 1 week	4466.4	(3095.2, 6445.0)
Month 61	5714.0	(3829.7, 8525.4)
HPV 18		
Month 7	741.2	(576.8, 952.4)
Month 60 (pre-challenge)	44.7	(31.8, 62.8)
Month 60 + 1 week	1033.2	(753.9, 1415.8)
Month 61	1230.0	(904.5, 1672.5)

Olsson, Villa, Costa, Petta, Andrade & Malm et al., 2007

Abstract

Objective: Infection with various types of HPV has a causal relationship with the development of cervical cancer and other anogenital diseases. A prophylactic quadrivalent HPV vaccination has been produced. Here the pathophysiology of HPV infection and results of multiple HPV vaccine studies are discussed to determine efficacy and immunogenicity.

Methods: The review includes articles found through PubMed and MEDLINE that focus on the infection with human papillomavirus, cervical cancer, and the HPV vaccine. **Results:** An HPV

vaccine has effectively been produced that has proven to decrease the incidence of cervical cancer and other anogenital diseases. The vaccine has been approved for use in women between the ages of 9 and 26 years of age for prevention of anogenital pathology. Five year follow-up studies of the vaccine have shown long-term efficacy and the induction of an immune memory

response. **Conclusion:** Studies to date have shown that the HPV vaccine is effective in reducing cervical cancer but it is still too early to know the full extent of vaccine efficacy. Future studies are necessary to continue monitoring the vaccine. In the meantime it is essential to maintain current cervical screening programs and promote patient education.